12. (Amended) The method of claim 1, wherein the route of administration of said phosphorothioate or active metabolite thereof is intravenous, intraperitoneal, intradermal, intramusculararal, dermal, nasal, buccal, rectal, vaginal, inhalation, or topical.

13. (Amended) The method of claim 1, wherein said phosphorothioate or active metabolite thereof is formulated into solutions, suspensions, tablets, pills, capsules, sustained release formulations, powders, creams, ointments, salves, sprays, pumps, liposomes, suppositories, inhalers, or patches.

A marked up copy of these amendments are illustrated in Appendix A attached hereto.

II. RESPONSE TO OFFICE ACTION

A. State of the Claims

Claims 1-31 were originally filed in this application. In response to a Restriction Requirement dated May 31, 2001, Applicants elected Group V, corresponding to claims 1-13 and 23-31. Claim 2 has been cancelled in the Amendment submitted herewith without prejudice or disclaimer. Claims 1, 8-13 have been amended. Claims 14-22 have been cancelled without prejudice or disclaimer. Support for the amended claims can be found in the claims as filed, and consequently, no new matter has been added to this application. Thus, claims 1-13 and 23-31 are the subject of this response. A copy of the pending claims can be found in Appendix B.

B. Amendments of the Specification

Applicants have amended the Specification to claim priority to a U.S. Provisional Application Serial Number 60/125,605 filed on 03/19/1999. Applicants note the inventor declarations filed on 09/08/2000 in this case reflect this priority claim. (Appendix F)

C. The Rejections Under 35 U.S.C. § 112, Second Paragraph, Are Overcome

1. Claims 8 and 11-13 have been amended and contain the requisite antecedent basis

The Action rejects claims 8 and 11-13 under 35 U.S.C. § 112, second paragraph, stating that there is insufficient antecedent basis for the limitation in the claims. Specifically, the Action stated that these claims recite the limitation "said compound" without sufficient antecedent basis for this limitation in the claims. Claims 8 and 11-13 have been amended to recite "phosphorothioate" which has sufficient antecedent basis in claim 1. Accordingly, the rejections of claims 8 and 11-13 on this ground are overcome.

2. Claims 9 and 10 have been amended and contain the requisite antecedent basis

The Action rejects claims 9 and 10 under 35 U.S.C. § 112, second paragraph, stating that there is insufficient antecedent basis for the limitation in the claims. Specifically, the Action stated that these claims recite the limitation "said derivative" without sufficient antecedent basis for this limitation in the claims. Claims 9 and 10 have been amended to recite "aminoalkylphosphorothiate," for which there is sufficient antecedent basis in amended claim 8. Accordingly, the rejections to claims 9 and 10 on this ground are overcome.

3. Claims 1-13 and 23-31 are complete

The Action rejects claims 1-13 and 23-31 under 35 U.S.C. § 112, second paragraph, stating that the claims are incomplete for omitting essential steps, such omission amounting to a gap between the steps. Specifically, the Action states that the omitted steps are: whether the phosphorothioate or active metabolite thereof reduces the number of metastases after administration into the animal in the claims 1-13 and 23-29. Applicants respectfully traverse.

Claim 1 teaches a method for reducing the number of metastases in an animal exhibiting a primary tumor comprising administering to said animal a subcytoprotective dose of a phosphorothioate or active metabolite thereof. The Action states that the omitted step is whether the phosphorothioate or active metabolite thereof reduces the number of metastases after administering into the animal.

Applicants point out that the *results* are not part of the method and thus the omission of the results does not amount to a gap between the steps. Thus, "Whether the phosphorothioate or active metabolite thereof reduces the number of metastases after the administration into the animal" is not a step in the current invention but is the *result* of applying the steps of the invention. Moreover, this limitation does not alter the steps a person of ordinary skill in the art would perform to practice the claimed invention; as such, it is a superfluous recitation. The steps of the invention pertaining to the *method* of reducing the number of metastases in an animal by administering a subcytoprotective dose of a phosphorothioate or active metabolite thereof is found in claim 1. Furthermore the steps of the invention pertaining to the method of monitoring the ability of the subcytoprotective dose of a phophorothioate or active metabolite to reduce metastases in the animal is found in claim 23. Applicants submit that the steps in claims 1 and 23 of the invention, cover the subject matter pertaining to the use of a phosphorothioate or active metabolite thereof to reduce the number of metastases in said animal. The claims cited are thus complete and are not omitting any essential steps resulting in a gap between the steps. Accordingly, the rejections of claims 1-13 and 23-31 on this ground are overcome.

4. Claims 1-13 and 23-31 are not vague because of the phrase "active metabolite"

The Action rejects claims 1-13 and 23-31 under 35 U.S.C. § 112, second paragraph, stating that the claims are indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the Action stated that the phrase "active metabolite thereof" in claims 1, 23, 30 and 31 is vague and renders the claims indefinite. The Action further states that it is unclear what "activity" is intended by the Applicants in the present application.

Applicants state that the phrase "active metabolite" is well understood to those of ordinary skill in the art, and furthermore, the specification states the "phrase 'active metabolite' is used according to its ordinary meaning among those of skill in the art, i.e., to refer to a product of intermediary metabolism that possesses an activity." Specification page 6, lines 28-30. The specification goes further to explain the phrase in the context of this particular invention at page 8, line 6; the activity of an active metabolite of a phosphorothioate is described as being able to reduce metastases in an animal. The definition of "active metabolite" in the specification is consistent with what is commonly understood by those of skill in the art, as exemplified by definition provided at www.behavenet.com, which states, "When a metabolite of a drug produces a therapeutic effect it is considered an active metabolite." (Appendix C). Accordingly, the rejections to claims 1, 23, 30 and 31 on this ground have been overcome.

D. The Rejections Under 35 U.S.C. § 102 Are Overcome

1. Claims 1, 7-9 and 11-13 are not anticipated by Milas et al., 1984 (IDS-C51)

The Action rejects claims 1, 7-9 and 11-13 under 35 U.S.C. 102(b) as being anticipated by Milas *et al.*, 1984 (IDS-C51). Specifically the Action recites that Milas anticipates the

present invention by teaching that amifostine (WR-2721) can greatly reduce the spontaneous metastases induced by cyclophosphamide (CY) and whole body irradiation (WBI) in mice that had been injected i.v. with fibrosarcoma. The Action alleges that WR-2721 was given intraperitoneally at a dose of 400 mg/kg and was capable of significant protection against metastases enhancement induced by CY and WBI. Applicants respectfully traverse these rejections.

Anticipation under section 102 is only valid when a reference shows exactly what is claimed; where there are differences between the references disclosures and the claim, a rejection must be based on obviousness under Section 103. *Richardson v. Suzuki Motor Co., Ltd.*, 868 F.2d 1226, 9 USPQ2d 1913 (Fed. Cir. 1989). Applicants present amended claims 1, 12 and 13 along with their dependent claims, which recite a dose range of "10 mg/kg to 150 mg/kg." Milas *et al.* does not teach a dose range of 10 mg/kg to 150 mg/kg; instead it teaches a dose of 400 mg/kg, which does not meet the limitations of the rejected claim. Moreover it would not be obvious to derive the present invention from Milas *et al.* as the report of Kanclerz and Chapman shows that treatment with a single 400mg/kg dose of WR-2721 *promoted* lung metastases (Kanclerz and Chapman, 1988) (Appendix D). Based on the results reported in Kanclerz and Chapman, a person of ordinary skill in the art would not think to use WR-2721 to remove metastases. Thus, Milas *et al.* does not anticipate the present invention.

Therefore, Applicants respectfully submit that rejection of claims 1, 7-9 and 11-13 under 35 U.S.C. 102(b) as being anticipated by Milas *et al.*, 1984 are overcome and should be withdrawn.

2. Claims 1, 8, 9, 12, 13, 30 and 31 are not anticipated by Flora et al. 1996

The Action rejects claims 1, 8, 9, 12, 13, 30 and 31 under 35 U.S.C. § 102 as being anticipated by *Flora et al.*, 1996 (IDS-C9). Specifically the Action argues that Flora teaches that N-acetylcysteine (NAC) is a promising cancer chemopreventative agent that acts through a variety of mechanisms, including its nucleophilic and antioxidant properties. Furthermore, the Action asserts that NAC is an aminophosphorothioate compound. Applicants respectfully traverse.

As previously stated anticipation under section 102 is only valid when a reference shows exactly what is claimed. Claims 1, 8, 9, 12, 13, 30 and 31 all specify the method for reducing the number of metastases in an animal by administering a subcytoprotective dose of a phosphorothioate, aminoalkylphosphorothioate, or active metabolite thereof. The Action contends that Flora *et al.* teaches the use of NAC, an amino alkylphosphorothioate compound, as a promising cancer chemopreventive that can inhibit lung metastases. A phosphorothioate is a molecule with one end containing a S-PO_3H_2, hence the term "phosphoro." The general formula for phosphorothioates is: $RHN(C_{[n]}H_{2n})NH(C_{[n]}H_{2n})SPO_3H_2$ wherein R is hydrogen or an alkyl group and each n is from 2 to 6, and hydrates or alkali metal salts thereof. *See* U.S. Patent No. 3,892,824 (Appendix E). NAC (N-acetylcysteine) is an analogue and precursor of reduced glutathione (Albini *et al.* Int. J. Cancer 61:121-129, 1995). The molecular formula of NAC is $C_5H_9NO_3S$. NAC does not contain a "phosphoro" group and therefore is not a phosphorothioate or a member of the phosphorothioate class. Since NAC is not a phosphorothioate, Flora *et al.* does not teach each element of the current invention, as is required for anticipation.

Accordingly, Applicants respectfully submit that rejection of claims 1, 8, 9, 12, 13, 30 and 31 under 35 U.S.C. § 102 on this ground is overcome and request it be withdrawn.

3. Claims 1, 7-9, 9, 12, 13, 30 and 31 are not anticipated by Hasegawa et al. 1998 (International Journal of Cancer, Vol. 76, No. 6, p. 812-816)

The Action rejects claims 1, 7-9, 12, 13, 30 and 31 under 35 U.S.C. § 102(a), as being anticipated by Hasegawa *et al.* 1998 (International Journal of Cancer, Vol. 76, No. 6, p. 812-816). Specifically, the action stated that Hasegawa *et al.* teaches injecting intraperitoneally the matrilysin-specific antisense phosphorothioate oligonucleotide at a maximum concentration of 120 μg/mouse into nude mice every day, from 1 day before to 10 days after the intrasplenic injection of WiDr cells (human colon carcinoma cells). The reported results are alleged to show strong inhibition of metastatic tumor nodules formation that was dose-dependent. Applicants respectfully traverse.

As previously stated anticipation under section 102 is only valid when a reference shows exactly what is claimed. Applicants present amended claims 1, 30 and 31, which now include a dose range of 10 mg/kg to 150 mg/kg. Hasegawa *et al.* does not teach a dose range of 10 mg/kg to 150 mg/kg; instead it teaches a dose of 120 μg/ mouse, which does not meet the limitations of the rejected claim. Claims 1, 30 and 31 all specify a method "for reducing the number of metastases in an animal by administering a subcytoprotective dose of 10 mg/kg to 150 mg/kg of a phosphorothioate, or active metabolite thereof." The Action contends that Hasegawa *et al.* teaches the use of matrilysin-specific antisense phosphorothioate oligonucleotide at a maximum concentration of 120 μg/ mouse. The rough approximation of phosphorothioate oligonucleotide dose reported by Hasegawa *et al.* is less than 0.120 mg/kg of phosphorothioate injected into each mouse. This approximation does not take into consideration the molecular weight of the oligonucleotide, which comprises the majority of the molecular weight of a phosphorothiate oligonucleotide, and thus, the exact dose would be substantially lower than 0.120 mg/kg. Thus even at a dose amount of 0.120 mg/kg, the dose range of the present invention is two orders of

magnitude greater than the dose reported in Hasegawa *et al.* Therefore, Hasegawa *et al.* does not teach the limitations of Applicant's claims.

Accordingly, Applicants respectfully submit that rejection of claims 1, 7-9, 12, 13, 30 and 31 under 35 U.S.C. § 102(a) on this ground are overcome.

E. The Rejections Under 35 U.S.C. § 103 Are Overcome.

1. Claims 2-7, 10, 23, and 25-29 are not obvious over Albini et al., in view of Golub, Grdina, Antras-Ferry, and Ullrich

The Action rejects claims 2-7, 10, 23, and 25-29 under 35 U.S.C. §103(a) as being unpatentable over Albini *et al.*, 1995 (IDS-C1), in view of Golub, 1998 (US Patent No. 5,837,696), Grdina *et al.*, 1995 (IDS-C15), Antras-Ferry *et al.*, 1997 (IDS-C2). The Action also raises issues with respect to the reference of Ullrich *et al.* The Action contends Albini *et al.* teaches thiol N-acetylcysteine (NAC) as a phosphorothioate and one of the most promising cancer chemopreventive agents. However, it acknowledges that Albini *et al.* does not specifically teach using the dose cited in the claims 2-5. Instead, the Action contends that Golub *et al.* teaches a dosage range of 0.1 mg/kg to 30 mg/kg, which is said to overlap with the range of 10 mg/kg to 150 mg/kg used in the present invention. Golub is also said to teach a method of inhibiting metastasis, in a mammal by administering to said mammal a cancer-inhibitory amount of a tetracycline compound. The Action then contends that it would be obvious for one of ordinary skill at the time of the invention to use the dose range cited in claims 2-5 for the claimed method because Golub teaches using a cancer-inhibitory amount of a tetracycline compound to inhibit metastasis of cancer cells. The Action also asserts that Golub teaches MMP expression especially gelatinase expression, which allegedly is associated with cancer

invasiveness or metastasis, and suggests detection of MMP gene products for a prophylactic treatment using tetracycline compound. Furthermore, the Action contends that it would have been obvious to monitor the ability of the phosphorothioate to reduce metastasis by measuring the stimulation of MnSOD gene expression.

The Action asserts that Grdina *et al.* teaches that WR-2721 and related aminothiols are radioprotective agents that provide protection against radiation induced mutagenesis. Furthermore, it contends that the anti-cytotoxic and anti-mutagenic mechanisms of action observed for WR-2721 are due to the thiol and disulfide metabolites of WR-2721. The Action contends that Antras-Ferry *et al.* teaches Oltipraz (4-methyl-5-(2-pyrazinyl)-1,2-dithiole-3-thione) (OPZ) as a potent chemoprotective agent against chemical induced carcinogenesis in several animal models and that OPZ induces the transcription of the manganese superoxide dismutate (MnSOD). Applicants respectfully traverse the rejection of the claims over Albini *et al.*, Golub, Grdina *et al.*, Antras-Ferry *et al.*

Finally, the Action asserts that Ullrich *et al.* teaches that WR-2721 can decrease the metastatic spread in tumor bearing mice after irradiation. It is not clear as to which claim(s) the action is rejecting over Ullrich *et al.*, irrespective of this matter, Applicants contend that the claims are nonobvious over Ullrich *et al.*

To establish a *prima facie* case of obviousness, three basic criteria must be met: (1) There must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (2) there must be a reasonable expectation of success; and (3) the prior art reference (or references when combined) must teach or suggest all the claim limitations. *Manual of Patent Examining Procedure* § 2142. *See also In re Vaeck*, 947 F.2d 488, 20

U.S.P.Q. 2d 1438 (Fed Cir. 1991) (emphasizing that the teaching or suggestion to make the claimed combination and the reasonable expectation of success must be both found in the prior art, and not based on applicant's disclosure). In response to all of the above objections Applicants submit that a proper *prima facie* case has not been made and provide the following replies to the rejections.

a. The cited references do not teach all the elements of the claims

With regard to Albini *et al.*, Applicants respectfully note that a valid *prima facie* case of obviousness requires that the cited prior art reference (or references when combined) teach or suggest all the claim limitations. Albini *et al.* is said to teach that NAC is a chemopreventative agent. However, the disclosure of NAC does not teach the claim limitation of phosphorothioates, as discussed previously, which is recited in each of the rejected claims. Hence, Albini *et al.* in combination with any of the other cited references does not make obvious or suggest any of the claims of the present invention.

b. There is no suggestion or motivation to combine references

As mentioned previously, "obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art." MPEP §2143.01. *See also In re Fine*, 837 F.2d at 1074, *In re Jones*, 958 F.2d at 351. The Action contends that a person of ordinary skill in the art would combine the dosages of Golub, which allegedly teaches the use of tetracyclines to inhibit metastasis, with the claimed invention. However, there is no reason a person of skill in the art would substitute *phosphorothioates* specifically for tetracycline because nothing in Golub, Albini *et al.*, or any of the other cited references suggests the combination of

the teachings of the cited references. Arguably, combining the references of Golub and Albini *et al.* results in a method of inhibiting metastasis by administering the tetracyclines of Golub with the dosages of Albini *et al.* Established patent law sets out that "[i]t is impermissible within the framework of 35 U.S.C. § 103 to pick and choose from any on reference only so much of it as will support a given position to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one skilled in the art." *Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve, Inc.*, 230 U.S.P.Q. 416 (Fed. Cir. 1986). By relying upon certain portions of the reference without any reason, the Action is impermissibly "picking and choosing" from the references.

Furthermore, there is no suggestion or motivation to combine the reference of Grdina *et al.* with any of the cited references. Grdina *et al.* is alleged to teach that WR-2721 and related aminothiols are radioprotective agents that provide protection against radiation induced mutagenesis. There is no suggestion or motivation in Grdina *et al.* to combine it with the teaching of Golub, that is, to administer these compounds at "subcytoprotective" doses, particularly the doses of "10 mg/kg to 150 mg/kg ," as recited in all of the rejected claims. By contending that a person of ordinary skill in the art would combine the references of Albini *et al.*, Golub, and Grdina *et al.*, the Examiner is seeking to employ impermissible hindsight in reconstructing the elements necessary to achieve the invention piecemeal from the prior art. *See Loctite Corp. v. Ultraseal Ltd.*, 781 F.2d 861, 873 (Fed.Cir.1985). The Federal Circuit has repeatedly held that such hindsight reconstruction is an improper basis for a §103 rejection. *See id.* Thus, all of the claims have been improperly rejected on this basis.

Furthermore, rejection of any claims based on the cited references in combination with Antras-Ferry is also improper, as Antras-Ferry does not remedy the defects in the *prima facie*

case. Antras-Ferry is said to teach OPZ as a potent chemoprotective agent against chemical induced carcinogenesis in several animal models. There is no basis for combining it with the other references. If anything, it teaches *away* from the claimed invention because it involves OPZ, while the present invention concerns a phophorothioate administered in a subcytoprotective dose. Any rejection of claims based on Albini *et al.*, Golub, Grdina *et al.*, and/or Antras Ferry is improper because a valid *prima facie* case was not made.

c. Ullrich *et al* does not render obvious any claims by itself or in combination with any other cited reference

The Action confusingly refers to the reference of Ullrich *et al.* in the middle of its grounds for an obviousness rejection but does not identify it as the basis for the rejection. The Action also does not state whether it is being combined with any references and to which claims it is relevant. Nonetheless, Applicants contends that Ullrich *et al.* does not render obvious any of the claims either by itself or in combination with any other reference cited in the Action.

The Action contends Ullrich *et al.* teaches that WR-2721 decreases the metastatic spread in tumor bearing mice after irradiation. A proper *prima facie* case cannot be made with reference because there is no motivation to combine references. The claims recite a "subcytoprotective dose of 10 mg/kg to 150 mg/kg of a phosphorothioate." Ullrich does not teach such a *subcytoprotective* dose—a dose that is below the level that will confer protection—and in fact, specifically states that a WR2721 "did protect the normal tissues included in the radiation field." Ullrich *et al.* at page 2. In further confirmation of this point, Applicants point out that Ullrich *et al.* employed a dose of 400 mg/kg. There is nothing in the reference that indicates its teaching should be combined with any of the other cited teachings. Moreover, this reference is evidence that a person of ordinary skill in the art *would not* be motivated to combine

references to achieve the recited dosage levels to achieve what the preamble sets out. Thus, this reference does not support a *prima facie* obviousness rejection of the claims.

Applicants submit that the rejections of claims 2-7, 10, 23, and 25-29 under 35 U.S.C. §103(a) are overcome.

2. *Claim 24 is patentable over Albini et al., 1995 (IDS-C1), in view of Gately et al., 1997 (IDS-C13)*

The Action rejects claim 24 under 35 U.S.C. §103(a) as being unpatentable over Albini *et al.*, 1995 (IDS-C1), in view of Gately, 1997 (IDS-C13). The Action states that it would have been obvious for one of ordinary skill in the art at the time of the invention to measure the stimulation of angiostatin for monitoring the ability of the phosphorothioate or active metabolite thereof because angiostatin was known to suppress lung carcinoma metastasis and the stimulation of angiostatin would indicate the reduction of metastases. Applicants respectfully traverse.

As discussed earlier, a *prima facie* case of obviousness requires that the prior art reference (or references when combined) teach or suggest all the claim limitations. *MPEP* § 2142. Again, Albini *et al.* does not teach a phosphorothioate as recited by the claims because NAC is not a phosphorothioate. As previously discussed NAC does not contain a "phosphoro" group and therefore is not a phosphorothioate or a member of the phosphorothioate class. Thus, Albini *et al* does not teach all the limitations of the current invention. Furthermore, since NAC is not a phosphorothioate and there is no suggestion that a phosphorothioate could be used in place of NAC, it would not be obvious nor suggestive to one of ordinary skill in the art to combine specifically Albini *et al.* with Gately *et al.* to arrive at the present invention. The Federal Circuit held in *In re Mills*, 916 F.2d 680, 682 (Fed. Cir. 1990), that the mere fact that combination or modification of a reference or references is possible does not establish

obviousness of the resultant combination unless the prior art also suggests the desirability of the combination, *i.e.*, unless the prior art provides motivation to produce the resultant combination. *Id.*; *see also* MPEP § 2143.01, page 2100-91. This, the references do not do. Accordingly, the rejections to claim 24 on this ground are overcome.

CONCLUSION

It is submitted that in light of the foregoing remarks, the invention embraced by the pending claims has been shown to be patentable, and favorable reconsideration is earnestly solicited.

The Examiner is invited to contact the undersigned attorney at 512-536-3081 with any questions, comments or suggestions relating to the referenced patent application.

Respectfully submitted,

Gina N. Shishima
Reg. No. 45,104
Attorney for Applicants

FULBRIGHT & JAWORSKI L.L.P.
600 Congress Avenue, Suite 2400
Austin, Texas 78701
(512) 474-5201
(512) 536-4598 (facsimile)

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